STABILIZATION OF RETINOID COMPOUNDS

CROSS-REFERENCE

This application claims priority from provisional application serial number 60/262,687 filed on January 19, 2001.

FIELD OF THE INVENTION

The present invention relates to the topical delivery of retinoid compounds.

BACKGROUND OF THE INVENTION

Retinoic acid is a retinoid sold both for the topical treatment of acne (Retin-A®, Ortho Dermatological, Skillman, New Jersey) and for the topical treatment of fine wrinkles, mottled hyperpigmentation, and tactile roughness of facial skin (Renova®, Ortho Dermatological). The compound is formulated into a variety of topical gels, creams, and solutions.

U.S. Patent No. 5,726,191 recently reported a new class of retinoids. According to the '191 Patent, these compounds can be topically administered in ointments, tinctures, creams, solutions, lotions, sprays, and suspensions. Applicants, however, have found that while members of this class of compounds were very potent in binding to the retinoid receptor, they are chemically unstable in topical formulations.

In fact, applicants tested Compound I, a compound from this class, in a vast array of topical liquid or semisolid pharmaceutical formulations. None of these formulations, however, were capable of sufficiently stabilizing the compound when stored at room temperature (between 20 to 30°C), thus, inhibiting the ability to market the compound in a topical formulation.

The present invention relates to stabilizing this new class of retinoids in a manner suitable for topical administration.

SUMMARY OF THE INVENTION

In one aspect, the invention features a method of administering a compound of Formula I (defined herein), wherein the method includes the step of admixing the compound in solid form with a topical carrier to form a topical formulation within seven days prior to first topical administration of the compound.

In another aspect, the invention features a kit comprising two chambers, wherein the first chamber contains a compound in solid form and the second chamber contains a topical carrier in an amount capable of dissolving or dispersing said compound where the compound is of Formula I.

Other features and advantages of the present invention will be apparent from the detailed description of the invention and from the claims.

DETAILED DESCRIPTION OF THE INVENTION

It is believed that one skilled in the art can, based upon the description herein, utilize the present invention to its fullest extent. The following specific embodiments are to be construed as merely illustrative, and not limitative of the remainder of the disclosure in any way whatsoever.

Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which the invention belongs. Also, all publications, patent applications, patents, and other references mentioned herein are incorporated by reference.

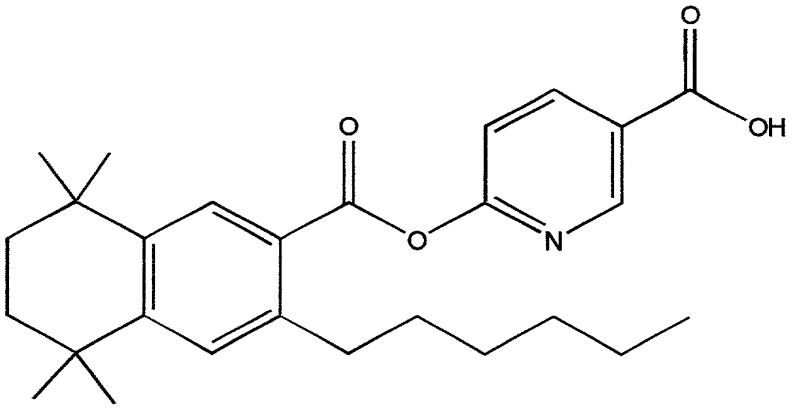
sufficient for a single application of the compound). In a further embodiment, the topical carrier comprises an alcohol. Examples of such alcohols include, but are not limited to, the group consisting of ethanol, isopropyl alcohol, and propylene glycol. In one embodiment, the topical carrier further includes an gelling agent. In one-embodiment, the gelling agent is an oil-soluble gelling agent. Suitable gelling agents for oils (such as mineral oil) include, but are not limited to, hydrogenated butylene/ethylene/styrene copolymer and hydrogenated ethylene/propylene/styrene copolymer. Such gels typically comprises between about 0.1% and 5%, by weight, of such gelling agents.

In another embodiment, the method includes admixing multiple unit dosages of the compound. In a further embodiment, the topical carrier comprises a member selected from the group consisting of diisopropyl adipate, diisopropyl sebacate, diisocetyl adipate, triacetin, caprylic/capric triglyceride, and isopropyl myristate. In a further embodiment, the method further includes the step of refrigerating the resulting formulation during the course of administration of the multiple unit dosages.

In one embodiment, the method further comprises admixing the formulation containing the compound with a cream (e.g., a water-in-oil emulsion or oil-in-water emulsion) or a gel (e.g., an aqueous, petrolatum, or silicone gel).

In another aspect, the invention features a kit comprising two chambers, wherein the first chamber contains the compound in solid form and the second chamber contains a topical carrier in an amount capable of dissolving or dispersing said compound where the compound is of Formula I.

In one embodiment, the topical carrier is in an amount capable of substantially dissolving the compound.



Compound III

Other examples of compounds of formula I are:

6-(3-hexyl-5,5-dimethyl-6,7,8,9-tetrahydro-5H-benzocyclohepten-2- yl-carbonyloxy)-nicotinic acid,

6-(3-hex-1-enyl-5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-naphthalen- 2-yl-carbonyloxy)-nicotinic acid,

6-(6-hexyl-3,3-dimethyl-indan-5-yl-carbonyloxy)-nicotinic acid,

6-(3-butoxy-5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-naphthalen-2- yl-carbonyloxy)-nicotinic acid,

6-(3-adamantan-1-yl-4-hydroxy-benzoyloxy)-nicotinic acid,

6-(3-hexanoyl-5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-naphthalen-2- yl-carbonyloxy)-nicotinic acid, and

6-(3-hexyl-5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-naphthalen-2-yl- carbonylsulphanyl)-nicotinic acid.

Methods of manufacturing compounds of the present invention are set forth in U.S. Patent No. 5,726,191.

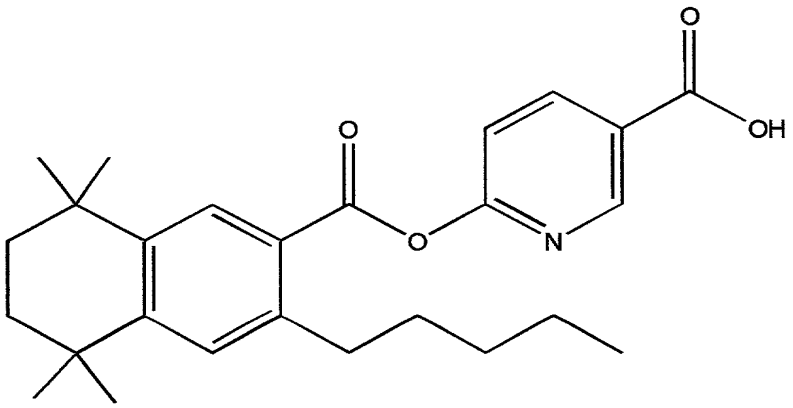
In one embodiment, the topical carrier substantially dissolves said compound (e.g., dissolves at least 90% of the compound). In one embodiment, the topical carrier suspends the compound. In one embodiment, the composition comprises about 0.001% to about 1%, by weight, of the compound (e.g., about 0.01% to about 0.1%, by weight).

In one embodiment, the method includes admixing a unit dose of the compound (e.g., an amount of the compound

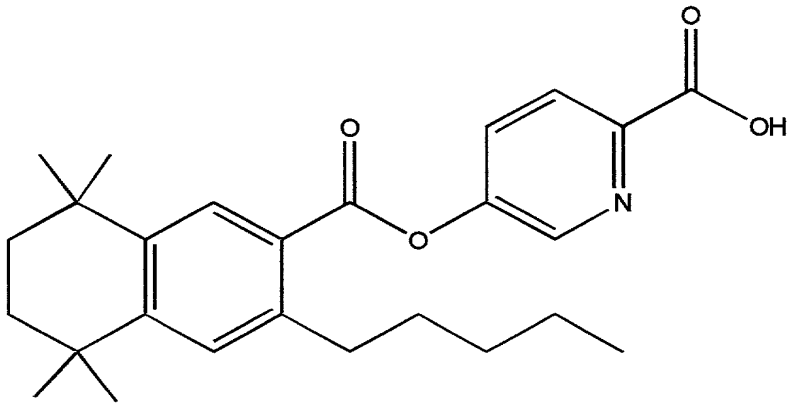
2-propynyl and 1- and 2-butynyl are examples of alkynyl residues. Examples of C_{2-8}-alkanoyl residues are straight-chain alkanoyl residues such as acetyl, propionyl, butyryl, pentanoyl, hexanoyl, heptanoyl and octanoyl.

In one embodiment of the invention the pyridine-carboxylic acid residue in the compounds of Formula I is a nicotinic acid residue, that is, when R^1 is hydrogen (e.g., a nicotinic acid residue linked in the 5- or 6-position). In one embodiment, R^2 and R^3 taken together are $-(CR^6R^7)_n-$. In a further embodiment, R^2 and R^3 taken together are $-C(CH_3)_2CH_2CH_2C(CH_3)_2-$, $-C(CH_3)_2(CH_3)_2-$, or $-C(CH_3)_2(CH_2)_4-$. In one embodiment, Y is oxygen. In one embodiment, R^4 is C_{2-8}-alkyl. In one embodiment, R^1 is hydrogen.

Examples of compounds of Formula I are the following:

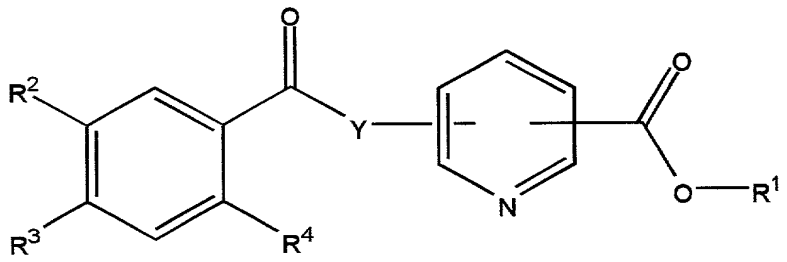


Compound I



Compound II

In one aspect, the present invention relates to a method of administering a compound of Formula I



Formula I

wherein

R^1 is hydrogen or C_{1-6}-alkyl;

R^2 is C_{1-6}-alkyl or adamantyl;

R^3 is C_{1-6}-alkyl or hydroxy; or

R^2 and R^3 taken together are $-(CR^6R^7)_n-$;

R^4 is C_{2-8}-alkyl, C_{2-8}-alkenyl, C_{2-8}-alkynyl, $-OCH_2R^5$ or C_{2-8}-alkanoy, or hydrogen when R^3 is hydroxy;

R^5 is C_{1-6}-alkyl, C_{2-6}-alkenyl or C_{2-6}-alkynyl;

R^6 and R^7 are hydrogen or C_{1-6}-alkyl;

Y is oxygen or sulfur; and

n is 3, 4, or 5,

or a pharmaceutically acceptable salts of the carboxylic acid of formula I.

The notations "C_{1-6}", "C_{2-6}", and "C_{2-8}" used herein stand for groups with from 1 to 6, from 2 to 6 and from 2 to 8 carbon atoms, respectively. Alkyl residues can be straight-chain or branched. The alkyl residues of R^1 may be straight-chain such as methyl, ethyl, propyl, butyl, pentyl and hexyl. Alkyl residues of R^2 and R^3 may be branched alkyl residues such as tert-butyl. Alkyl residues of R^4 and R^5 may be straight-chain such as ethyl, propyl, butyl, pentyl, and hexyl. Examples of alkenyl residues are straight-chain alkenyl residues such as vinyl, 1- and 2- propenyl, and 2-butenyl. Ethynyl, 1- and

In one embodiment, the topical carrier is in an amount capable of suspending the compound.

In one embodiment, the first chamber contains a unit dose of the compound. In a further embodiment, the topical carrier contains an alcohol. In a further embodiment, the second chamber further contains a gelling agent.

In one embodiment, the first chamber contains multiple unit dosages of the compound. In a further embodiment, the solvent is selected from the group consisting of diisopropyl adipate, diisopropyl sebacate, diisocetyl adipate, triacetin, caprylic/capric triglyceride, and isopropyl myristate. In a further embodiment, the kit further includes a label instructing the user to refrigerate the compound following dissolution.

In one embodiment, the kit further comprises a third chamber containing a cream (e.g., a water-in-oil emulsion or oil-in-water emulsion) or a gel (e.g., an aqueous, petrolatum, or silicone gel).

In one embodiment, the first chamber and second chamber are separate containers (e.g., vials). The contents of one container may then be added and admixed with the contents of the other container (e.g., the compound may be removed from its container and added and admixed with the topical carrier in its container). In a further embodiment, the resulting mixture is administered by using a wipe applicator that may or may not be stored within the other container. Examples of such administration is well known in the art, e.g., Benzamycin® topical gel.

In another embodiment, the two chambers are within the same container, but are separated by a wall that is breakable upon the application of force. Examples of two chamber packages for delivery of unit dosages are well known in the art and are available from supplier such as Klocke Verpackungs GmbH (Weingarten, Germany). In a further

embodiment, the resulting mixture is administered by using a wipe applicator that may or may not be stored within the container.

Unit dosages may also be administered using applicator stick wherein the topical carrier is stored within the shaft of the applicator and separated from the applicator end of stick by a breakable wall. The compound of Formula 1 is contained within the applicator end of the stick (e.g., a foam or fabric tip). Upon rupturing the breakable wall, the topical carrier enters the foam head and dissolves/suspends the compound. Examples of such applicators are well known in the art, e.g., Betadine PrepStick™ applicator (Purdue Frederick, Norwalk, CT).

The compounds of the present invention are useful in the treatment or prevention of skin disorders such as acne, psoriasis, photo-damage, environmental damage, intrinsic age damage, wrinkles, tumors (e.g., melanomas), hyperpigmentation, and skin roughness. The compounds of the present invention may also be used for the promotion of wound healing. Other uses of the present invention are set forth in U.S. Patent No. 5,726,191.

As discussed above, compounds of the present invention were found to be chemically unstable once formulated into a topical carrier. What is meant by a topical carrier is a liquid or semi-solid formulation capable of being applied topically to the skin. Examples of topical carriers include, but are not limited to, ointments, sprays, creams, lotions (e. g., solutions, suspensions and emulsions), or gels. The topical carrier is preferably anhydrous.

Thus, in order to ensure stability of such compounds, they must be stored in solid form, and then reformulated into a topical carrier proximate to the time of first application (e.g., within seven days prior to the first topical administration of said compound). In one embodiment, the compound is reformulated within forty-

eight (48) hours prior to first topical administration of said compound. In one embodiment, the compound is mixed by a doctor, pharmacist, or by the end user.

The following is a description of the manufacture of various topical formulations of the present invention. Other formulations of the invention can be prepared in an analogous manner by a person of ordinary skill in the art.

Example 1:

The stability of Compound I was tested in the following twenty-eight different topical formulations, set forth in Table 1. Finsolv® TN is a C12-15 alkyl benzoate from Fintex, Inc. (Elmwood Park, NJ) Miglyol® 812 from Huls AG (Marl, Germany) and Neobee® 1053 from Stepan Company (Northfield, IL) are each a caprylic/capric triglyceride.

Table 1

Formulation No.	Carrier	Volume %
Formulation 1	Diisopropyl sebacate	100
Formulation 2	Diisopropyl sebacate	60
	Cyclomethicone	40
Formulation 3	Miglyol® 812	100
Formulation 4	Isopropyl laurate	100
Formulation 5	Diisopropyl sebacate	50
	Isopropyl laurate	50
Formulation 6	Diisopropyl adipate	50
	Cyclomethicone	50
Formulation 7	Diisopropyl adipate	100
Formulation 8	Diisopropyl adipate	50
	Isopropyl laurate	50
Formulation 9	Propylene glycol	100
Formulation 10	PEG 400	100
Formulation 11	Propylene carbonate	100

Formulation 12	Dimethyl isosorbide	100
Formulation 13	Miglyol® 812	100
Formulation 14	Finsolv® TN	100
Formulation 15	Glycerin	100
Formulation 16	Isopropyl myristate	100
Formulation 17	Cyclomethicone	100
Formulation 18	Dimethicone	100
Formulation 19	Mineral oil	100
Formulation 20	Sunflower oil	100
Formulation 21	Soybean oil	100
Formulation 22	Neobee® 1053	100
Formulation 23	Sesame oil	100
Formulation 24	Butyl Acetate	100
Formulation 25	Isopropanol	100
Formulation 26	PEG 400	30
	Ethanol	70
Formulation 27	Triacetin	100
Formulation 28	Tributyrin	100

The general procedure to prepare the above formulations is as follows. A 500 mg of Compound 1 was weighed and transferred into an 800 ml glass beaker containing 500 g of one of the above carriers. The formulation was then stirred with a paddle mixer (stirrer type RZR50 from Caframo in Wiarton, Ontario, Canada) at 100 RPM setting until the compound was completely dissolved/dispersed in the carrier.

About 20 g each of the resulting formulations were then packed into 24 clear glass scintillation vials of 20ml volume (Wheaton Disposable Scintillation Vials from Wheaton Scientific in Milleville, NJ) and labeled. Groups of eight of such vials were then stored at 4°C, RT (22°C) and/or 40°C for stability studies.

The samples of the formulations at each of the above three temperatures were then periodically analyzed for the

chemical stability of Compound 1. The compound was assayed using high performance liquid chromatographic (HPLC) system. The results of this analysis is set forth in Table 2 setting forth the amount of Compound 1 remaining in the formulation following a certain number of days at specified temperatures. Chemical degradation of Compound 1 was seen in all of the formulations stored at 22°C and/or 40°C, thus, demonstrating a need to make the formulation proximate to the time of administration and/or refrigerate the formulation after it is made.

Table 2

Formulation No.	Days	% Remaining		
		4°C	22°C	40°C
Formulation 1	84	102	89	64
Formulation 2	84	101	90	68
Formulation 3	56	100	93	60
Formulation 4	56	100	97	87
Formulation 5	56	100	96	80
Formulation 6	90	87	84	63
Formulation 7	90	87	80	57
Formulation 8	90	100	93	69
Formulation 9	36	82.39	--	0.71
Formulation 10	36	93.56	--	0.71
Formulation 11	70	100.77	--	40.18
Formulation 12	18	96.84	--	65.36
Formulation 13	70	93.46	--	49.09
Formulation 14	36	100.48	--	2.23
Formulation 15	29	97.44	--	84.09
Formulation 16	22	95.43	--	86.18
Formulation 17	85	100	--	83
Formulation 18	30	98.16	--	76.18
Formulation 19	70	104.83	--	84.83
Formulation 20	70	102.20	--	51.83
Formulation 21	22	101.34	--	83.82

Formulation 22	21	100	97.38	88.62
Formulation 23	23	102.66	--	86.77
Formulation 24	34	100	--	55.48
Formulation 25	18	100	80.79	5.96
Formulation 26	13	100	86.74	9.13
Formulation 27	23	100	96.41	93.81
Formulation 28	22	100	97.49	86.08

It is understood that while the invention has been described in conjunction with the detailed description thereof, that the foregoing description is intended to illustrate and not limit the scope of the invention, which is defined by the scope of the appended claims. Other aspects, advantages, and modifications are within the claims.

What is claimed is: